Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Guimarães PO, Quirk D, Furtado RH, et al. Tofacitinib in patients hospitalized with Covid-19 pneumonia. N Engl J Med. DOI: 10.1056/NEJMoa2101643

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S3. Supplemental Methods:

S3.1 Timing of RT-PCR Assay

Participants with laboratory confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as determined by a positive reverse-transcriptase-polymerase chain reaction (RT-PCR), who had agreed to participate, were screened within 72 hours after hospital admission to determine eligibility. The original protocol (version 1.0 of June 23, 2020), which was submitted for approval by the healthcare authorities, did not establish a time window between symptom onset and RT-PCR collection for Covid-19 diagnosis confirmation. When the protocol was reviewed by ANVISA (The National Regulatory Agency from Brazil), it was suggested that RT-PCR should be collected after a minimum of 3 days from symptom onset, due to test sensitivity. Therefore, the protocol was amended on August 24, 2020 (version 2.0) to reflect this addition. Recruitment started after that. Subsequently, it was brought to our attention by some of the study sites that they were missing potential patients who had symptoms of Coronavirus disease 2019 (Covid-19) and had a RT-PCR collected during routine clinical practice before they were hospitalized. Since these patients could not be included because of the protocol version approved at the time, they considered that these criteria represented a potential barrier for recruitment. The Steering Committee discussed these suggestions and feedback from the sites, and considered that patients with confirmed diagnosis of Covid-19 by a positive RT-PCR would be eligible for the trial if they were hospitalized, had chest computed tomography or a chest X ray compatible with Covid-19 pneumonia, and fulfilled all the other eligibility criteria. In order words, we considered that it would not make sense to exclude these patients and that they could potentially benefit from participating in the trial. Therefore, the protocol was further amended on Sep 22, 2020 (version 3.0) to allow the possibility to also include patients who had a positive RT-PCR (collected during routine practice) before trial procedures had started, regardless of the time from symptom onset. These patients were only included after the amendment was approved by health care authorities. Of note, a total of 61 (21.3%) patients had the qualifying RT-PCR with less than 3 days of symptom onset. The median time from symptom onset to Covid-19 diagnosis was 4 (IQR 3 to 7) days.

S3.2 Inclusion and Exclusion Criteria

The inclusion criteria were the following:

- Male or female participants older than 18 years;
- Laboratory-confirmed SARS-CoV-2 infection as determined by RT-PCR prior to day 1;
- Evidence of Covid-19 pneumonia assessed by radiographic imaging (chest x-ray or chest computed tomography scan);
- Hospitalization for less than 72 hours and receiving standard of care treatment for Covid-19.

The diagnostic criteria were based on guidance from the World Health Organization, in which confirmed cases of SARS-Cov-2 infection were those confirmed by molecular tests with viral sequencing or real-time quantitative RT-PCR of swab samples obtained from nasopharyngeal, bronchoalveolar lavage, nasopharyngeal tracheal aspirate, blood, serum and tissue from lung biopsies specimens.

The exclusion criteria were the following:

- Need for noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) on day 1;
- History of or known current thrombosis. Only if current thrombosis was suspected by the investigator, imaging testing was recommended to exclude thrombosis before enrollment;
- Personal or first-degree family history of blood clotting disorders;
- Patients who were immunocompromised, with known immunodeficiencies, or taking potent immunosuppressive agents (e.g., azathioprine, cyclosporine);
- Any current malignancy or lymphoproliferative disorders that required active treatment;
- Severe hepatic impairment, defined as Child-Pugh class C;
- Severe anemia (hemoglobin <8 g/dL);
- An absolute lymphocyte count <500 cells/mm^3;
- An absolute neutrophil count <1000 cells/mm^3;
- Known allergy to tofacitinib;
- Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that might increase the risk associated with study participation or, in the investigator's judgment, make the participant inappropriate for the study;
- Suspected or known active systemic bacterial, fungal, or viral infections (with the exception of Covid-19) including but not limited to: active herpes zoster infection; known active tuberculosis or history of inadequately treated tuberculosis; known hepatitis B, hepatitis C, or human immunodeficiency virus;
- Patients who had received any of the following treatment regimens specified in the timeframes outlined below within 4 weeks prior to the first dose of study intervention: any Janus kinase

(JAK) inhibitors, potent immunosuppressants, or any biologic agents including interleukin (IL)-6 inhibitors (e.g., tocilizumab) or IL-1 inhibitors (e.g., anakinra) within the past 30 days; any potent cytochrome P450 inducer, such as rifampin, within the past 28 days or 5 half-lives, whichever was longer;

- Patients who had received any of the following treatment regimens specified in the timeframes outlined below within 48 hours prior to the first dose of study intervention: estrogen-containing contraception or treatment with herbal supplements;
- Patients who had received treatment with glucocorticoids equivalent to prednisone or methylprednisolone >20 mg/day for equal or more than 14 consecutive days prior to screening;
- Patients who were current participants in other clinical trials.

S3.3 Choice of Study Drug Regimen

The choice of the study drug regimen (tofacitinib 10 mg BID) was based on its expected effect on inflammation in a short-term setting whereas there was no apparent short-term, dose-dependent increase in the risk for adverse events. Tofacitinib 5 and 10 mg BID have been extensively studied in multiple clinical development programs including the approved indications for rheumatoid arthritis, ulcerative colitis and psoriatic arthritis. At the 10 mg BID, plasma tofacitinib concentrations are maintained above the half maximum inhibitory concentration for IL-6 inhibition throughout a 24-hour dosing interval at steady-state, unlike the lower dose of 5 mg BID. In a prior study with rheumatoid arthritis patients, the onset of pharmacologic activity of tofacitinib 10 mg after the first dose was within 4 hours. In addition, in patients with rheumatoid arthritis or psoriasis, the 10 mg BID dose regimen provided substantially higher suppression of systemic inflammatory markers when compared with the 5 mg BID dose regimen.

Importantly, the safety profile of tofacitinib 10 mg BID is well characterized. Short-term exposure to tofacitinib 10 mg BID has not been associated with a significantly increased risk of infection or thrombosis when compared to 5 mg BID. The time to first reported thrombotic event in the tofacitinib clinical development program of patients treated with tofacitinib 10 mg BID was well beyond the 14-day treatment duration. The STOP-COVID protocol also incorporated risk minimization measures for the potential thrombotic risk in the Covid-19 setting. Taken together, the short-term treatment with tofacitinib 10 mg BID was expected to provide better and faster anti-inflammatory effects for controlling potential increases in cytokine activity and progression to acute respiratory distress syndrome in Covid-19 patients than the 5 mg BID dose regimen.

S3.4 Reasons for Discontinuation of Study Intervention

Reasons for definitive discontinuation of study intervention included the following: white blood count <1000 cells/mm^3; lymphocyte count <250 cells/mm^3; absolute neutrophil count <500 cells/mm^3; hemoglobin <8 g/dL; alanine aminotransferase or aspartate aminotransferase ≥5 times the upper limit of normal; anaphylaxis or other serious allergic reaction; diagnosis of thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis; participants who developed contraindications for anticoagulation treatment; and any serious infection or other safety event for which the investigator determined that continuing treatment with tofacitinib was not in the participant's best interest.

S3.5 Adverse Events

Adverse events were assessed by review of the electronic medical records, physical examinations, vital signs, and laboratory studies from the time the informed consent form was signed through day 28. AEs were classified in accordance with the Medical Dictionary for Regulatory Activities (MedDRA version 23.1), and their relationship to study product, severity, and outcome were documented. All serious adverse events (SAEs) were captured in this trial. Adverse events of special interest (AESIs) were the following: serious infections (excluding Covid-19) leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections and viral reactivation; lymphomas and other malignancies; thrombosis, including pulmonary, deep venous or arterial thrombosis; gastrointestinal perforation; interstitial lung disease; cardiovascular events; and clinically significant changes in lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids. All AESIs were reported with the same criteria as SAEs.

S3.6 Additional Statistical Analysis Details

The following analysis populations were defined for statistical analyses: a) full analysis set (FAS) including all participants randomly assigned to study intervention, considering the treatment which he was allocated to; and b) safety analysis set (SAS) considering all participants randomly assigned to study intervention and who took at least 1 dose of study intervention, considering the actual treatment. All

efficacy statistical analyses were performed based on the FAS population, and the safety analyses were based on the SAS population.

Demographics and baseline characteristics were summarized for each treatment group. Categorical variables are presented as relative and absolute frequencies. Continuous variables are summarized using mean and standard deviation or median and interquartile range. The primary outcome was initially the occurrence of death or respiratory failure at day 28. However, it was changed to the occurrence of death or respiratory failure through day 28 since the cumulative incidence of these events during the 28 days was deemed to be more clinically meaningful than the event rate at only one specific timepoint. This change was proposed by the Executive Committee who was unaware of treatment assignments and had no knowledge of outcome data, and before the interim analysis was conducted by the DSMB. The amendment was finalized on December 3, 2020, and the initial primary outcome was retained as a secondary outcome.

The primary outcome was analyzed by binary regression with Firth correction, with the treatment and inclusion of antiviral therapy for Covid-19 as covariates. Sensitivity analyses were performed through logistic regression with Firth correction, with the treatment and inclusion of antiviral therapy as covariates, and also through binary regression with the inclusion of glucocorticoids as a covariate. Additionally, the primary outcome was analyzed using mixed models with estimation via the model builder algorithm for the study site as random effects. This algorithm optimizes, via Laplace approximations, the marginal likelihood integrated with the random effects. The duration of hospitalization and intensive care unit hospitalization were analyzed treating death as a competing risk, and results are expressed as median (interquartile range) and hazard ratios (95% confidence intervals). Duration of mechanical ventilation was analyzed by difference in medians.

Originally, we planned an interim analysis for futility, to be conducted when the data for the primary endpoints (including either completion of Day 28 visit or death) became available in approximately 40% of the participants. However, owing to faster-than-expected enrollment, primary-outcome data for the futility interim analyses were available only after completion of enrollment, while follow-up was still ongoing. After discussion with the data and safety monitoring board (DSMB), the interim analysis for futility was deemed to be unnecessary. Therefore, the DSMB conducted safety analyses only and recommended that the trial should continue as planned.

S4. Supplemental Figures and Tables:

S4.1 Figure S1. Kaplan-Meier Curves for the Primary Outcome in Patients with Baseline Ordinal Scale of 4

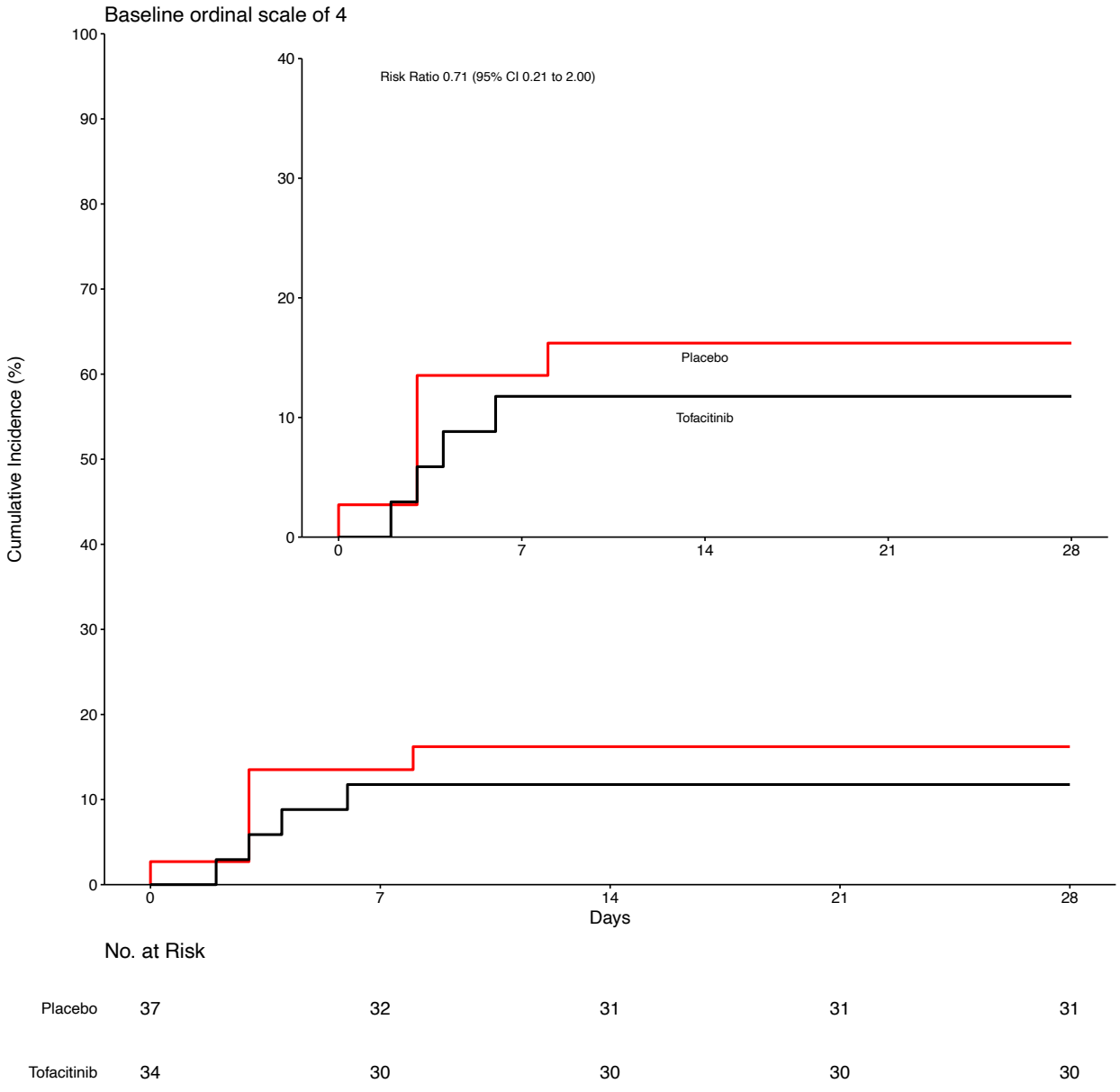

Figure legend. The risk ratio for the primary outcome was calculated from binary regression with Firth correction, with the treatment and inclusion of antiviral therapy for Covid-19 as covariates. The inset shows the same data on an expanded Y axis. Category 4 indicates patients who were hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19-related or otherwise). CI denotes confidence interval.

S4.2 Figure S2. Kaplan-Meier Curves for the Primary Outcome in Patients with Baseline Ordinal Scale of 5

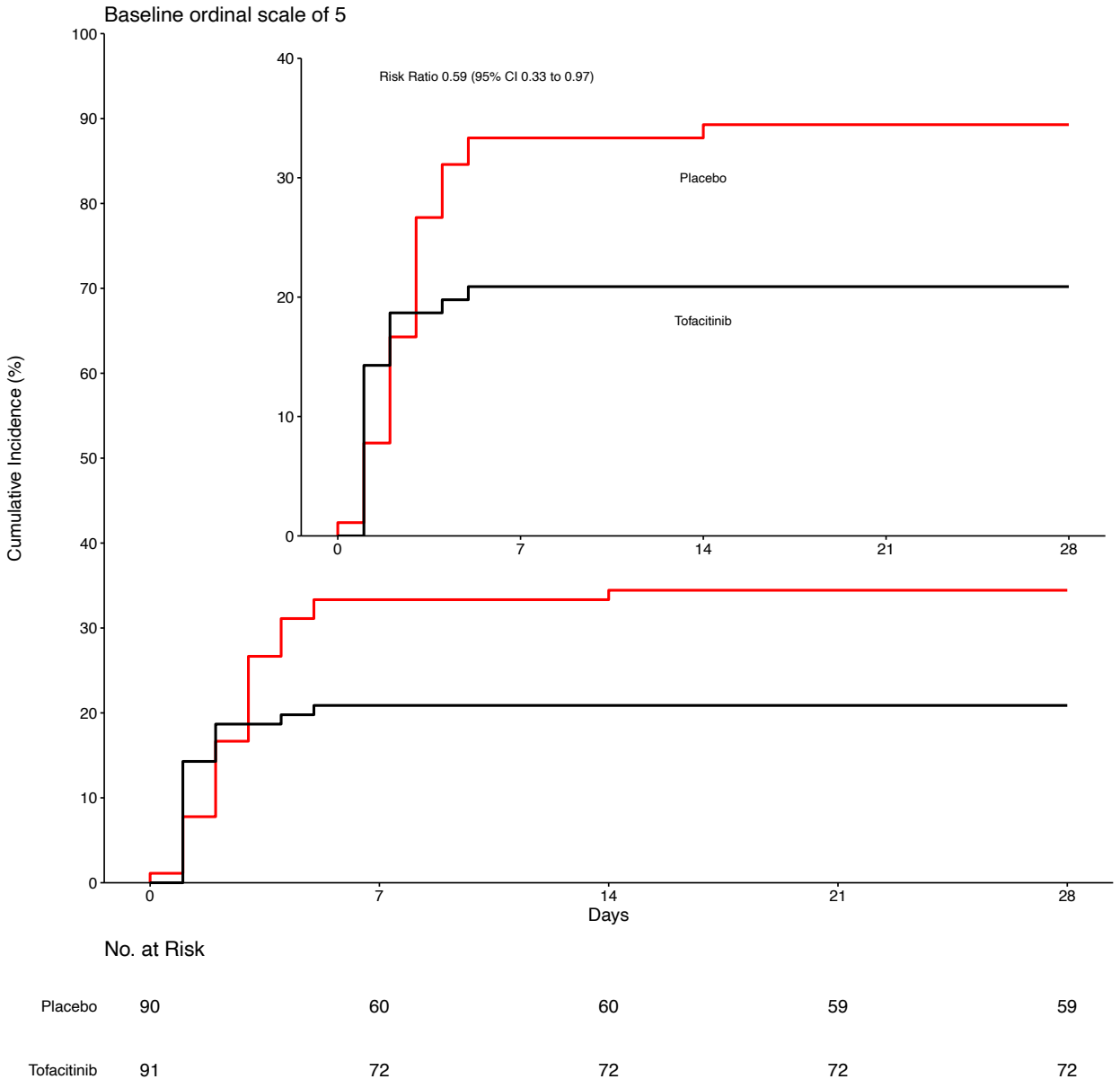

Figure legend. The risk ratio for the primary outcome was calculated from binary regression with Firth correction, with the treatment and inclusion of antiviral therapy for Covid-19 as covariates. The inset shows the same data on an expanded Y axis. Category 5 indicates patients who were hospitalized, requiring supplemental oxygen by low-flow devices. CI denotes confidence interval.

S4.3 Figure S3. Kaplan-Meier Curves for the Primary Outcome in Patients with Baseline Ordinal Scale of 6

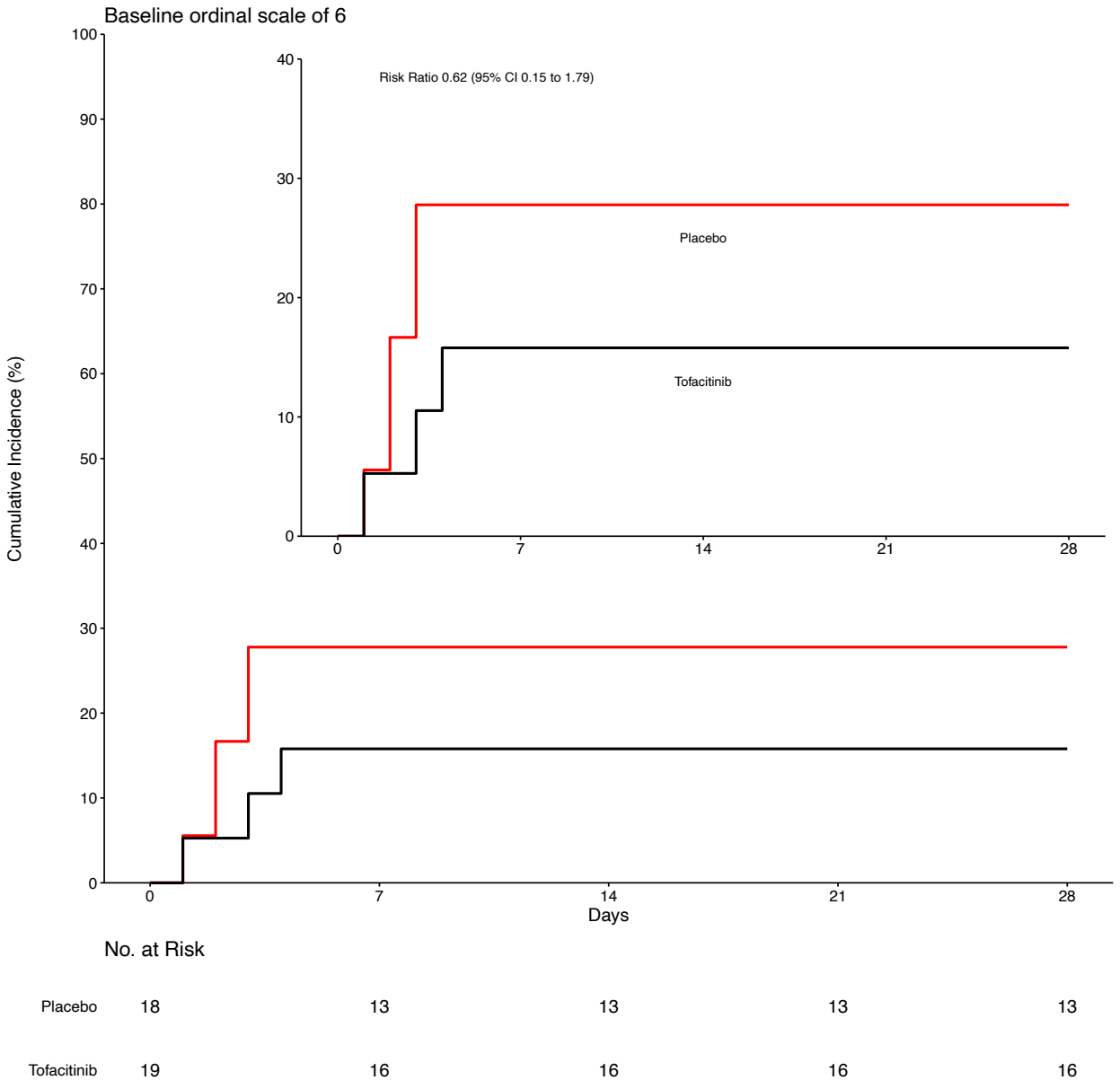

Figure legend. The risk ratio for the primary outcome was calculated from binary regression with Firth correction, with the treatment and inclusion of antiviral therapy for Covid-19 as covariates. The inset shows the same data on an expanded Y axis. Category 6 indicates patients who were hospitalized, on non-invasive ventilation or on high-flow oxygen devices. CI denotes confidence interval.

S4.4 Figure S4. Kaplan-Meier Curves for Death

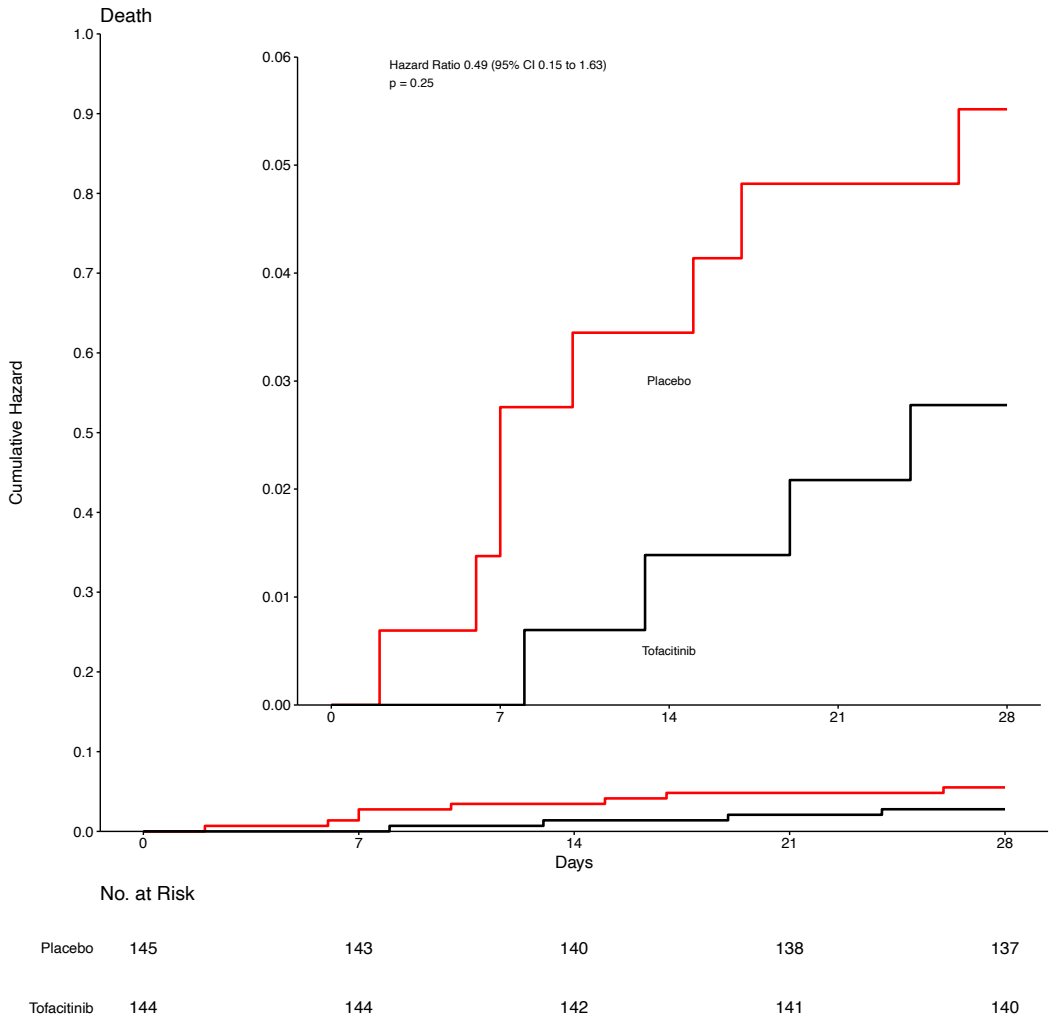

Figure legend. The cumulative proportion of patients was estimated with the Kaplan–Meier method and a Cox proportional-hazards model was used to estimate the hazard ratio and 95% confidence interval (CI). The inset shows the same data on an expanded Y axis.

S4.5 Figure S5. Clinical Status at 14 Days and 28 Days

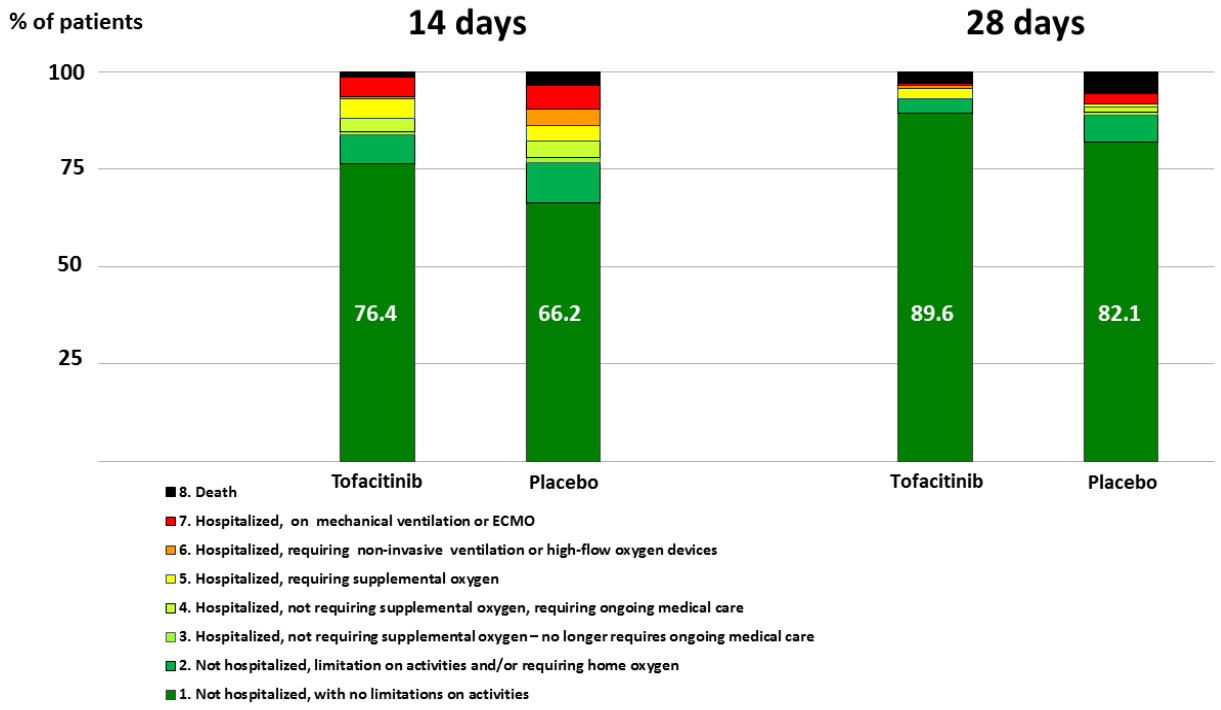

Figure legend. Categories on the eight-category ordinal scale range from 1 to 8, with higher categories indicating a worse condition. Category 1 indicates that the patient was not hospitalized, with no limitations on activities; 2, was not hospitalized but had limitation on activities and/or required home oxygen; 3, was hospitalized, not requiring supplemental oxygen – no longer required ongoing medical care; 4, was hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care (Covid-19-related or otherwise); 5, was hospitalized, requiring supplemental oxygen by low-flow devices; 6, was hospitalized on non-invasive ventilation or high-flow oxygen devices; 7, was hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation; and 8, died.

S4.6 Table S1. Ordinal Scale

1	Not hospitalized, with no limitations on activities.
2	Not hospitalized, limitation on activities and/or requiring home oxygen.
3	Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care.
4	Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19-related or otherwise)
5	Hospitalized, requiring supplemental oxygen by low-flow devices
6	Hospitalized, on non-invasive ventilation or on high-flow oxygen devices
7	Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation
8	Death

S4.7 Table S2. Study Drug Exposure

	All Patients (N = 289)	Tofacitinib (N = 144)	Placebo (N = 145)
Number of days using study drug, median (IQR)*	6 (4 to 9)	5 (3 to 8)	6 (4 to 10)
Number of participants who used at least one dose of study drug within 14 days, no. (%)	284 (98.3)	142 (98.6)	142 (97.9)
Number of participants who were compliant to the study regimen, median (IQR)*†	270 (95.1)	134 (94.4)	136 (95.8)
Number of participants who received reduced dose since the trial beginning, no. (%)*‡	25 (8.8)	11 (7.7)	14 (9.9)
Number of participants who received reduced dose during the trial, no. (%)*‡§	34 (12.0)	22 (15.5)	12 (8.5)
Number of participants with treatment withdrawal during the trial, no. (%)*¶	35 (12.3)	20 (14.1)	15 (10.6)
Number of participants who received the full-dose regimen (10 mg BID) continuously from randomization until death, hospital discharge, or day 14*	188 (66.2)	90 (63.4)	98 (69.0)

IQR, interquartile range.
*This analysis excludes 5 patients who did not receive any dose of study drug.
†To be compliant to the study regimen, the participant should have received between 70 and 120% of the maximum dose.
‡A reduced dose regimen of 5 mg twice daily was given for patients with an estimated glomerular filtration rate <50 mL/min/1.73 m^2, those with moderate hepatic impairment, and those with concomitant use of a strong CYP3A4 inhibitor, or a combination of a moderate CYP3A4 inhibitor and a strong CYP2C19 inhibitor at enrollment or at any time during the trial.
§ This analysis includes patients who initiated treatment with the full dose of study drug and had the dose reduced during the trial period.
¶ Reasons for definitive discontinuation of study intervention included the following: white blood count <1000 cells/mm^3; lymphocyte count <250 cells/mm^3; absolute neutrophil count <500 cells/mm^3; hemoglobin <8 g/dL; alanine aminotransferase or aspartate aminotransferase ≥5 times the upper limit of normal; anaphylaxis or other serious allergic reaction; diagnosis of thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis; participants who developed contraindications for anticoagulation treatment; and any serious infection or other safety event for which the investigator determined that continuing treatment with tofacitinib was not in the participant's best interest.

S4.8 Table S3. Use of Concomitant Treatments During Hospital Stay

Medication	**All Patients (N = 289)**	**Tofacitinib (N = 144)**	**Placebo (N = 145)**
Antibiotics	254 (87.9)	129 (89.6)	125 (86.2)
Macrolides	125 (43.3)	61 (42.4)	64 (44.1)
Quinolones	24 (8.3)	12 (8.3)	12 (8.3)
Beta-lactams	234 (81.0)	120 (83.3)	114 (78.6)
Others	20 (6.9)	8 (5.6)	12 (8.3)
Glucocorticoids	258 (89.3)	128 (88.9)	130 (89.7)
Dexamethasone	210 (72.7)	99 (68.8)	111 (76.6)
Methylprednisolone	72 (24.9)	39 (27.1)	33 (22.8)
Prednisone	22 (7.6)	10 (6.9)	12 (8.3)
Hydrocortisone	14 (4.8)	8 (5.6)	6 (4.1)
Oseltamivir	40 (13.8)	20 (13.9)	20 (13.8)
Anticoagulants	287 (99.3)	142 (98.6)	145 (100)
Hydroxychloroquine	5 (1.7)	2 (1.4)	3 (2.1)

* Data are presented as no. (%).

S4.9 Table S4. Major Protocol Deviations

	All Patients (N = 289)	**Tofacitinib (N = 144)**	**Placebo (N = 145)**
Number of patients who were randomized but did not meet inclusion or exclusion criteria, no. (%)*	3 (1.0)	1 (0.7)	2 (1.4)
Number of patients who received the wrong study treatment at any time during the study, no. (%)	0	0	0
Number of patients who received prohibited concomitant medication, no. (%)†	1 (0.3)	0	1 (0.7)

IQR, interquartile range.
*Three patients were randomized and had exclusion criteria: one had human immunodeficiency virus, one had history of thrombosis and one had lymphopenia.
†One patient received tocilizumab during the trial. Study drug was discontinued.

S4.10 Table S5. Sensitivity Analysis for the Primary Outcome

Outcome	Tofacitinib (N = 144)	Placebo (N = 145)	
Primary Outcome			**Odds Ratio (95% CI)**
Death or respiratory failure until day 28 – no. (%)*	26 (18.1)	42 (29.0)	0.54 (0.31 to 0.94)
			Risk Ratio (95% CI)
Death or respiratory failure until day 28 – no. (%)†	26 (18.1)	42 (29.0)	0.62 (0.41 to 0.95)
Death or respiratory failure until day 28 – no. (%)‡	26 (18.1)	42 (29.0)	0.61 (0.38 to 0.95)

CI, confidence interval.
*Results for the primary outcome were analyzed by logistic regression with Firth correction, with the treatment and inclusion of antiviral therapy for Covid-19 as covariates.
†Results for the primary outcome were analyzed with the inclusion of the use of glucocorticoids and antivirals at baseline as covariates.
‡Results for the primary outcome were analyzed with the use of a mixed model for adjustment for study sites.

S4.11 Table S6. Trial Outcomes Classified by the Ordinal Scale at Baseline

Outcome	Ordinal Scale at Baseline					
	4		5		6	
	Tofacitinib (N = 34)	Placebo (N = 37)	Tofacitinib (N = 91)	Placebo (N = 90)	Tofacitinib (N = 19)	Placebo (N = 18)
Primary Outcome						
Death or respiratory failure through day 28 – no. (%)*	4 (11.8)	6 (16.2)	19 (20.9)	31 (34.4)	3 (15.8)	5 (27.8)
Risk Ratio (95% CI)	0.71 (0.21 to 2.0)		0.59 (0.33 to 0.97)		0.62 (0.15 to 1.79)	
Secondary Outcomes						
Death through day 28 – no. (%)†	0 (0)	1 (2.7)	3 (3.3)	6 (6.7)	1 (5.3)	1 (5.6)
Hazard Ratio (95% CI)	NE		0.48 (0.12 to 1.93)		0.72 (0.04 to 12.03)	
NIAID ordinal scale at day 14– no (%)‡						
1	29 (85.3)	28 (75.7)	69 (75.8)	59 (65.6)	12 (63.2)	9 (50)
2	1 (2.9)	5 (13.5)	8 (8.8)	9 (10)	2 (10.5)	1 (5.6)
3	0 (0)	0 (0)	1 (1.1)	2 (2.2)	0 (0)	0 (0)
4	1 (2.9)	0 (0)	3 (3.3)	6 (6.7)	1 (5.3)	0 (0)
5	2 (5.9)	0 (0)	4 (4.4)	4 (4.4)	1 (5.3)	2 (11.1)
6	0 (0)	2 (5.4)	0 (0)	3 (3.3)	1 (5.3)	1 (5.6)
7	1 (2.9)	1 (2.7)	5 (5.5)	4 (4.4)	1 (5.3)	4 (22.2)
8	0 (0)	1 (2.7)	1 (1.1)	3 (3.3)	1 (5.3)	1 (5.6)
Odds Ratio (95% CI)	0.51 (0.15 to 1.77)		0.61 (0.32 to 1.15)		0.50 (0.13 to 1.86)	
NIAID ordinal scale at day 28– no (%)‡						
1	30 (88.2)	33 (89.2)	82 (90.1)	72 (80)	17 (89.5)	14 (77.8)

2	3 (8.8)	2 (5.4)	2 (2.2)	8 (8.9)	0 (0)	0 (0)
3	0 (0)	0 (0)	0 (0)	1 (1.1)	0 (0)	0 (0)
4	0 (0)	0 (0)	0 (0)	1 (1.1)	0 (0)	1 (5.6)
5	1 (2.9)	0 (0)	2 (2.2)	1 (1.1)	1 (5.3)	0 (0)
6	0 (0)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)
7	0 (0)	1 (2.7)	1 (1.1)	1 (1.1)	0 (0)	2 (11.1)
8	0 (0)	1 (2.7)	3 (3.3)	6 (6.7)	1 (5.3)	1 (5.6)
Odds Ratio (95% CI)	0.98 (0.22 to 4.43)		0.46 (0.19 to 1.09)		0.41 (0.06 to 2.82)	
Status of being alive and not using mechanical ventilation or ECMO (categories 1 to 6 of the ordinal scale) at day 14§	33 (97.1)	35 (94.6)	85 (93.4)	83 (92.2)	17 (89.5)	13 (72.2)
Risk Ratio (95% CI)	1.02 (0.83 to 1.05)		1.01 (0.90 to 1.06)		1.22 (0.79 to 1.35)	
Status of being alive and not hospitalized (categories 1 to 2 of the ordinal scale) at day 14§	30 (88.2)	33 (89.2)	77 (84.6)	68 (75.6)	14 (73.7)	10 (55.6)
Risk Ratio (95% CI)	1.00 (0.74 to 1.09)		1.12 (0.96 to 1.22)		1.30 (0.72 to 1.64)	
Status of being alive and not using mechanical ventilation or ECMO (categories 1 to 6 of the ordinal scale) at day 28§	34 (100)	35 (94.6)	87 (95.6)	83 (92.2)	18 (94.7)	15 (83.3)
Risk Ratio (95% CI)	1.05 (0.86 to 1.06)		1.03 (0.93 to 1.07)		1.12 (0.78 to 1.19)	
Status of being alive and not hospitalized (categories 1 to 2 of the ordinal scale) at day 28§	33 (97.1)	35 (94.6)	84 (92.3)	80 (88.9)	17 (89.5)	14 (77.8)
Risk Ratio (95% CI)	1.02 (0.83 to 1.05)		1.04 (0.92 to 1.09)		1.14 (0.74 to 1.26)	
Cure at day 28§ ¶	33 (97.1)	35 (94.6)	84 (92.3)	82 (91.1)	17 (89.5)	15 (83.3)
Risk Ratio (95% CI)	1.02 (0.83 to 1.05)		1.01 (0.89 to 1.07)		1.07 (0.69 to 1.18)	

CI denotes confidence interval; NE, not possible to estimate; NIAID National Institute of Allergy and Infectious Diseases.
* The risk ratio and the P value for the primary outcome were calculated from binary regression with Firth correction, with the treatment and inclusion of antiviral therapy for Covid-19 as covariates.
† The effect of the intervention on death until day 28 is expressed as hazard ratio (HR) derived from Cox regression.

‡ For ordinal data, a proportional odds model adjusted for inclusion of antiviral therapy at baseline was used. The assumption of proportional odds was met using the method of Pulkstenis-Robinson (p value for the 14-day analysis was 0.632, and for the 28-day analysis was 0.139). In this case, a p value higher than 0.05 indicates that the proportional-odds assumption was met. An odds ratio (OR) of less than one represents a clinical improvement with tofacitinib compared with placebo assessed on the ordinal scale. Categories on the eight-category ordinal scale range from 1 to 8, with higher categories indicating a worse condition. Category 1 indicates that the patient was not hospitalized, with no limitations on activities; 2, was not hospitalized but had limitation on activities and/or required home oxygen; 3, was hospitalized, not requiring supplemental oxygen – no longer required ongoing medical care; 4, was hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care (Covid-19-related or otherwise); 5, was hospitalized, requiring supplemental oxygen by low-flow devices; 6, was hospitalized on non-invasive ventilation or high-flow oxygen devices; 7, was hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation; and 8, died.
§ Risk ratios for secondary outcomes were calculated similarly to the primary outcome. A risk ratio of more than one represents a clinical benefit of tofacitinib compared with placebo.
¶ Cure refers to resolution of fever, cough, and need for ventilatory or oxygen support. A total of 2 patients did not have information on the date of symptom start, but had ordinal scale data at day 28. They were considered to have attained the outcome of cure since they did not need ventilatory or oxygen support at day 28.

S4.12 Table S7. Sensitivity Analysis for the Secondary Outcomes

Outcomes	**Tofacitinib (N = 144)**	**Placebo (N = 145)**	
			Odds Ratio (95% CI)*
Status of being alive and not using mechanical ventilation or ECMO (categories 1 to 6 of the ordinal scale) at day 14	135 (93.8)	131 (90.3)	1.57 (0.67 to 3.67)
Status of being alive and not hospitalized (categories 1 to 2 of the ordinal scale) at day 14	121 (84.0)	111 (76.6)	1.61 (0.90 to 2.90)
Status of being alive and not using mechanical ventilation or ECMO (categories 1 to 6 of the ordinal scale) at day 28	139 (96.5)	133 (91.7)	2.36 (0.85 to 6.57)
Status of being alive and not hospitalized (categories 1 to 2 of the ordinal scale) at day 28	134 (93.1)	129 (89.0)	1.63 (0.73 to 3.65)
Cure at day 28†	134 (93.1)	132 (91.0)	1.30 (0.56 to 3.01)

* Results for dichotomous outcomes were by logistic regression and expressed as odds ratios (ORs) and 95% confidence intervals (CI). Categories on the eight-category ordinal scale range from 1 to 8, with higher categories indicating a worse condition. Category 1 indicates that the patient was not hospitalized, with no limitations on activities; 2, was not hospitalized but had limitation on activities and/or required home oxygen; 3, was hospitalized, not requiring supplemental oxygen – no longer required ongoing medical care; 4, was hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care (Covid-19-related or otherwise); 5, was hospitalized, requiring supplemental oxygen by low-flow devices; 6, was hospitalized on non-invasive ventilation or high-flow oxygen devices; 7, was hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation; and 8, died.
† Cure refers to resolution of fever, cough, and need for ventilatory or oxygen support.

S4.13 Table S8. Additional Clinical Outcomes by Treatment Groups

	Tofacitinib (N = 144)	**Placebo (N = 145)**	**Subdistribution Hazard Ratio* (95% CI)**
Median length of initial hospitalization (IQR) – days	5.5 (3.0 to 8.25)	6.0 (3.0 to 11.0)	1.18 (0.94 to 1.48)
Median length of initial hospitalization at the ICU (IQR) – days†	5.0 (3.0 to 11.0)	5.0 (2.0 to 11.5)	1.11 (0.72 to 1.70)
			Difference in median (95% CI)
Median duration of mechanical ventilation (IQR) - days‡	12.5 (9.25 to 17.0)	12.0 (6.0 to 21.0)	1.00 (-7.0 to 7.0)

CI, confidence interval. ICU, intensive care unit; IQR, interquartile range.
*In this analysis, death was treated as a competing risk. Subdistribution hazard ratios greater than 1 indicates a higher chance of being discharged from the hospital for tofacitinib versus placebo.
†This analysis includes 88 participants who were admitted to intensive care units during the trial.
‡This analysis includes 25 participants who used mechanical ventilation during the trial.

S4.14 Table S9. Adverse Events by MedDRA Preferred Term and Treatment Group

MedDRA Preferred Term	Tofacitinib (N = 142) No. (%)	Placebo (N = 142) No. (%)	Total (N = 284) No. (%)
Any event	37 (26.1)	32 (22.5)	69 (24.3)
Acute respiratory failure	8 (5.6)	5 (3.5)	13 (4.6)
Transaminases increased	7 (4.9)	4 (2.8)	11 (3.9)
Anemia	3 (2.1)	6 (4.2)	9 (3.2)
Acute kidney injury	6 (4.2)	2 (1.4)	8 (2.8)
Hyperglycemia	5 (3.5)	2 (1.4)	7 (2.5)
Lymphopenia	4 (2.8)	2 (1.4)	6 (2.1)
Hepatic failure	2 (1.4)	0	2 (0.7)
Hyperkalemia	2 (1.4)	0	2 (0.7)
Abdominal pain	1 (0.7)	0	1 (0.4)
Acute myocardial infarction	1 (0.7)	0	1 (0.4)
Agitation	1 (0.7)	0	1 (0.4)
Anal hemorrhage	1 (0.7)	0	1 (0.4)
Anxiety	0	1 (0.7)	1 (0.4)
Aspiration	1 (0.7)	0	1 (0.4)
Atrial fibrillation	0	1 (0.7)	1 (0.4)
Back pain	1 (0.7)	0	1 (0.4)
Bronchospasm	0	1 (0.7)	1 (0.4)
Cardiogenic shock	0	1 (0.7)	1 (0.4)
Chronic obstructive pulmonary disease	0	1 (0.7)	1 (0.4)
Decreased appetite	0	1 (0.7)	1 (0.4)
Deep vein thrombosis	1 (0.7)	0	1 (0.4)
Drug withdrawal syndrome	1 (0.7)	0	1 (0.4)
Fatigue	1 (0.7)	0	1 (0.4)
Hematuria	0	1 (0.7)	1 (0.4)
Hemorrhagic stroke	0	1 (0.7)	1 (0.4)
Headache	1 (0.7)	0	1 (0.4)
Hypercalcemia	1 (0.7)	0	1 (0.4)
Hypertension	1 (0.7)	0	1 (0.4)
Hypervolemia	0	1 (0.7)	1 (0.4)
Hypoglycemia	1 (0.7)	0	1 (0.4)
Hypokalemia	0	1 (0.7)	1 (0.4)

Hypoxia	1 (0.7)	0	1 (0.4)
Insomnia	0	1 (0.7)	1 (0.4)
Multiple organ dysfunction syndrome	0	1 (0.7)	1 (0.4)
Myocarditis	1 (0.7)	0	1 (0.4)
Nausea	1 (0.7)	0	1 (0.4)
Phlebitis	1 (0.7)	0	1 (0.4)
Pseudomembranous colitis	0	1 (0.7)	1 (0.4)
Psychomotor hyperactivity	1 (0.7)	0	1 (0.4)
Pulmonary hypertension	1 (0.7)	0	1 (0.4)
Pyrexia	1 (0.7)	0	1 (0.4)
Seizure	1 (0.7)	0	1 (0.4)
Shock	0	1 (0.7)	1 (0.4)
Sinus tachycardia	0	1 (0.7)	1 (0.4)
Supraventricular tachycardia	0	1 (0.7)	1 (0.4)
Tongue edema	1 (0.7)	0	1 (0.4)
Ventricular tachycardia	1 (0.7)	0	1 (0.4)
Infections	7 (4.9)	8 (5.6)	15 (5.3)
Sepsis	3 (2.1)	2 (1.4)	5 (1.8)
Septic shock	2 (1.4)	2 (1.4)	4 (1.4)
Lower respiratory tract infection	1 (0.7)	2 (1.4)	3 (1.1)
Upper respiratory tract infection	2 (1.4)	0	2 (0.7)
Urinary tract infection	1 (0.7)	1 (0.7)	2 (0.7)
Tuberculosis	0	1 (0.7)	1 (0.4)

No. = number of subjects reporting at least one event. MedDRA, Medical Dictionary for Regulatory Activities.

S4.15 Table S10. Serious Adverse Events by MedDRA Preferred Term and Treatment Group

MedDRA Preferred Term	Tofacitinib (N = 142) No. (%)	Placebo (N = 142) No. (%)	Total (N = 284) No. (%)
Any event	20 (14.1)	17 (12.0)	37 (13.0)
Transaminases increased	6 (4.2)	4 (2.8)	10 (3.5)
Lymphopenia	4 (2.8)	1 (0.7)	5 (1.8)
Acute respiratory failure	2 (1.4)	2 (1.4)	4 (1.4)
Acute kidney injury	3 (2.1)	0	3 (1.1)
Hepatic failure	2 (1.4)	0	2 (0.7)
Acute myocardial infarction	1 (0.7)	0	1 (0.4)
Anemia	0	1 (0.7)	1 (0.4)
Aspiration	1 (0.7)	0	1 (0.4)
Cardiogenic shock	0	1 (0.7)	1 (0.4)
Deep vein thrombosis	1 (0.7)	0	1 (0.4)
Hemorrhagic stroke	0	1 (0.7)	1 (0.4)
Multiple organ dysfunction syndrome	0	1 (0.7)	1 (0.4)
Pulmonary hypertension	1 (0.7)	0	1 (0.4)
Seizure	1 (0.7)	0	1 (0.4)
Shock	0	1 (0.7)	1 (0.4)
Ventricular tachycardia	1 (0.7)	0	1 (0.4)
Infections	5 (3.5)	6 (4.2)	11 (3.9)
Sepsis	3 (2.1)	2 (1.4)	5 (1.8)
Lower respiratory tract infection	1 (0.7)	2 (1.4)	3 (1.1)
Septic shock	1 (0.7)	2 (1.4)	3 (1.1)
Urinary tract infection	1 (0.7)	0	1 (0.4)

No. = number of subjects reporting at least one event. MedDRA, Medical Dictionary for Regulatory Activities. The risk ratio for tofacitinib versus placebo on the occurrence of serious infections was 0.83 (95% CI 0.25 to 2.58).

S4.16 Table S11. Adverse Events Leading to Study Drug Discontinuation by MedDRA Preferred Term and Treatment Group*

MedDRA Preferred Term	**Tofacitinib (N = 142) No. (%)**	**Placebo (N = 142) No. (%)**	**Total (N = 284) No. (%)**
Any event	16 (11.3)	5 (3.5)	21 (7.4)
Transaminases increased	6 (4.2)	1 (0.7)	7 (2.5)
Lymphopenia	4 (2.8)	2 (1.4)	6 (2.1)
Deep vein thrombosis	1 (0.7)	0	1 (0.4)
Fatigue	1 (0.7)	0	1 (0.4)
Headache	1 (0.7)	0	1 (0.4)
Hepatic failure	1 (0.7)	0	1 (0.4)
Nausea and back pain	1 (0.7)	0	1 (0.4)
Tongue edema	1 (0.7)	0	1 (0.4)
Infections			
Lower respiratory tract infection	0	1 (0.7)	1 (0.4)
Tuberculosis	0	1 (0.7)	1 (0.4)

*This table includes the adverse events leading to study drug discontinuation for reasons other than death. Other reasons for study drug discontinuation included: patient decision (2 in the tofacitinib group and 4 in the placebo group), physician decision (1 in the placebo group), 2 patients were transferred to another hospital which was not a study site (1 in the tofacitinib group and 1 in the placebo group), 1 patient in the placebo group had human immunodeficiency virus which was an exclusion criteria. No. = number of subjects reporting at least one event. MedDRA, Medical Dictionary for Regulatory Activities.